

EXPERIMENTAL RADIATION CATARACT—ITS CLINICAL RELEVANCE*

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CATARACT is one of the primary interests of ophthalmologists, and more than 400,000 cataract operations are performed annually in the United States alone.¹ It is also one of the main causes of loss of vision. Fifteen to 16% of the blind population in this country and Canada are classified so because of cataracts. Yet, despite the attention that has been directed toward this problem, much remains unknown about the mechanisms of cataract formation.

Radiation cataracts are similar to other types of complicated cataracts, as well as to some senile types in terms of their appearance, development, and histopathology. As such, they have been most useful in attempting to understand the mechanism of the development of lens opacities in general.

X rays were discovered by Roentgen in 1895. Two years later Chaluppecky's^{2,3} work suggested that x rays might cause cataracts, although Chaluppecky himself was not convinced that the changes he observed were due to the radiation. It is now well established that ionizing radiation can produce lens opacities. The clinical appearance was described originally by Rohrschneider⁴ and later by Cogan, Donaldson, and Reese.⁵ Characteristically, the opacities initially appear centrally in the posterior subcapsular region of the lens and consist of small granules and vacuoles that tend to form a roughly circular opacity (Figure 1). The opacity, at times, may have a relatively clear center giving it a doughnut configuration. Observed by slit-lamp biomicroscopy, the opacity may have a yellowish or beaten-brass appearance. As posterior changes increase, granular opacities and vacuoles may appear in the anterior subcapsular region, usually centrally. Depending on the radiation dose, the opacities may remain

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Fig. 1. A slit-lamp photomicrograph of a typical human radiation cataract. The opacity is located in the posterior subcapsular region of the lens. Note that the cataract is plaque-like and made up of small vacuoles and dots.

stationary in the early stages with little effect on vision, develop slowly to an intermediate stage and remain stationary for years, or progress to a fully mature cataract. As more of the lens cortex becomes involved, the cataract becomes nonspecific and cannot be differentiated from other types.

Radiation cataract is a type of complicated cataract and as such can be confused with opacifications due to trauma, chronic uveitis, retinitis pigmentosa, various systemic diseases, and age. However, in most instances a careful history and ocular examination will allow a differential diagnosis to be made with considerable accuracy.

One of the main problems initially concerned the dose of radiation that would produce an opacity. In the early reported cases, the dose was difficult to assess, primarily due to the lack of accurate dosimetry. In spite of the extensive experimental work which had been done (see reviews by Desjardins⁶ and Poppe⁷) by the end of World War II the problem of quantification of the cataractogenic dose of ionizing radiation still remained unresolved. At that time approximately 81 cases of radiation

cataracts in humans had been reported.⁸⁻¹⁴ In only 13 of those cases was sufficient information provided to allow the dose to be calculated. Thus, by the 1950s the best estimates of the cataractogenic dose ranged from 500 rads to more than 1500 rads. With the increasing use of radiation in diagnosis and therapy it seemed essential to establish this dose more exactly.

A study was undertaken to collect as large a series of cases of radiation cataracts as possible, actually to measure the amount of radiation to the lens and to analyze the data.¹⁵ The research was directed at providing answers to a number of theretofore unknown questions: The minimum dose to the lens that would produce a cataract; the percent incidence of cataracts at increasing dosage levels; the effect of dose on the time of onset of a cataract; the effect of dose on the incidence of stationary or progressive opacities; the relative effects of single and divided treatments on the above; and the relative sensitivity of young and adult lenses.

Files dating back to 1925 at the Memorial Center, New York City, were searched, as were those of the Radiotherapy Department of the Edward S. Harkness Eye Institute, Columbia-Presbyterian Medical Center, New York City. A total of 100 cases of radiation cataract were found in which the radiation factors could be duplicated. In every instance the eyes were examined by an ophthalmologist and the diagnosis established by means of the ophthalmoscope and slit-lamp biomicroscope. A radiation cataract was defined as any clinically recognizable opacity having the characteristic appearance previously described, irrespective of whether or not vision was affected. Cases not subject to an ocular examination or in which the etiology was in question due to some complicating factor (previous surgery, trauma, hemorrhage or uveitis), or for which the dose to the lens could not be determined were excluded from this group. Also excluded were cases with peripheral dots or vacuoles in elderly patients where the possibility of early senile changes might compromise the accuracy of a diagnosis of radiation changes.

In addition to the individuals demonstrating radiation cataracts, 73 cases were found, all of whom had received measureable amounts of radiation to the head, but who did not develop lens opacities. All of these patients had had eye examinations from three years, one month to 28 years, six months after completion of treatment. Those who had follow-up examinations less than three years after therapy were excluded. The average time of the last ocular examination after therapy was eight years, 11 months. Thus, the initial study comprised a total of 173 cases, 100 with radiation

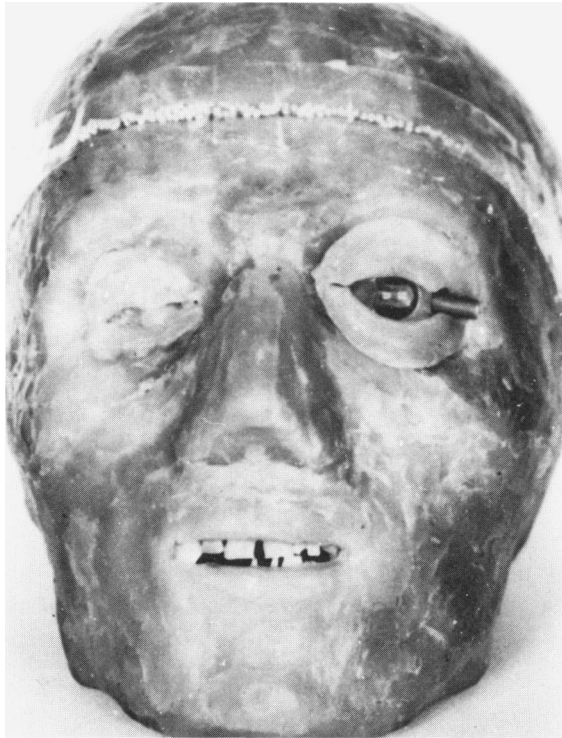


Fig. 2. The phantom used in the radiation studies was a human skull covered with a mixture of paraffin and beeswax and filled with bolus. Provision was made in the plastic eye to place a small Baldwin-Farmer Condenser ionization chamber in the position of the lens. Reproduced by permission from Merriam, G. R., Jr., and Focht, E. F.: A clinical study of radiation cataracts and the relationship to dose. *Am. J. Roentgenol.* 77:759-85, 1957.

cataracts and 73 without lens opacities. Subsequently other cases were found, resulting in a total of 233 cases, 128 with radiation cataracts and 105 without.

To determine accurately the actual amount of radiation to the lens for each case, a phantom (Figure 2) was devised employing a skull of average size covered with a unit-density mixture of paraffin and beeswax (equal parts by weight). The skull was coated in such a manner and thickness as to simulate normal skin and subcutaneous tissue and thus to approximate the scatter contribution to the eye from these structures. The cranial cavity was filled with bolus, a composition of sucrose and magnesium carbonate with electron density and effective atomic number within 1% of the value for water. The bolus has the same transmission qualities as water for 45 kVp through 1 MeV X- and gamma radiation. Plastic eyes of unit density

material were designed to accept a small Baldwin-Farmer condenser ionization chamber. The device, 6 mm. long and 5 mm. in diameter, was inserted into the position of the lens and could thus measure the dose of direct and scattered radiation that would be expected to be absorbed by this structure. The orbital apices were filled with wax so that the eyes were in their normal positions. Lids, also of wax, were made with a cut-out at the lateral canthus to allow insertion and removal of the chamber (Figure 2).

The phantom was treated as was each patient for all of the various types of lesions included in the series. These included hemangiomas of the lids, orbit, cheek and mouth, and various types of carcinomas of the lids, eye, nose, nasopharynx, sinuses, cheek, palate, and gum. In every case, the radiation factors, shielding, and positioning were reconstructed as closely as possible from data available in the chart, which usually included diagrams, photographs, or both. Each measurement was repeated several times.

The energy of the radiations ranged from 100 to 1200 kVp. Total doses varied from about 20 to 6,900 rads, and the radiation was applied in single doses or doses fractionated over periods of up to 10 years. The sample included both sexes, and ages ranged from one month to over 70 years. For analytical purposes the cases were arranged in three groups representing the most frequent courses of therapy: single treatments, multiple treatments from three weeks to three months, and multiple treatments over a period greater than three months.

Degree of opacity: Depending on the dose, a radiation-induced opacity may be small and stationary, with little or no visual impairment. Alternatively, it may progress, resulting in significant loss of vision. In a group of patients whose lenses received an average dose of 450 rads in a single treatment, one third developed progressive opacities. In a group whose lenses received an average dose of 800 rads, only one third had stationary opacities. When the total dose is fractionated, the lens tolerates a higher dose without progression of the cataract. Thus, with a single dose of 800 rads, two thirds of the cases had progressive opacities, whereas when this dose was delivered in three weeks to three months, only two fifths of the cataracts were progressive.¹⁵

Time of onset of cataract: The latent period (the interval between the time of treatment with X or gamma radiation to the time of the appearance of lens opacities) in humans had been estimated to be from 0.5 to 35 years, with an approximate average of two to three years. In a group exposed to a single dose of 450 rads, the average time at which cataracts

were first discovered was eight years and seven months following treatment. A similar group exposed to a dose of 800 rads showed an average time of onset of four years and four months. Fractionation of a dose delays the initial appearance of the opacities but the inverse relationship between the dose and the latent period remains. It is a tenet that the latent period between exposure and the appearance of a radiation cataract is an inverse function of dose.

DOSE-RESPONSE RELATIONSHIP

For the single treatment group, the lowest cataractogenic dose was found to be 200 rads. For the group with a treatment time of three weeks to three months, the minimum dose was 400 rads. If the treatment time exceeded three months, the lowest dose that caused cataracts was 550 rads.

If the data were analyzed in another way, by maximum dose that did not produce an opacity, a similar effect was found. In the single exposure group, the maximum noncataractogenic dose was 200 rads. In the group with a treatment time of three weeks to three months, the highest dose that did not produce an opacity was 1,000 rads. In the third group, with a treatment time greater than three months, the maximum noncataractogenic dose was 1,050 rads.¹⁵ These results suggest a time-dose relationship because, as the duration of treatment was increased, a higher dose was necessary to produce a given effect. Stated another way, the lens seemed able to tolerate a higher dose with increased fractionation and overall duration of treatment.

The time-dose relationship has been studied for many tissues.^{16,17} These studies showed that the slopes of the time-dose curves vary for different effects and tissues. Several reports in the literature suggested a lessened effect on the lens with fractionation of low LET (Linear Energy Transfer) radiation such as x rays.

The 233 clinical cases were plotted as overall treatment time versus dose according to the method of Strandqvist¹⁷ (Figure 3). Points for noncataract patients were plotted and a line drawn at the upper limit of these points. The cataract cases were plotted and a line drawn along their lower limits. Below the lower line are the noncataract cases and above the upper line those with cataracts. In the zone between are both cataract and noncataract cases. A dose delivered within a certain time that falls in the middle zone might or might not cause a cataract. Within this zone, the probability of a progressive cataract increases with increasing dose. Time-

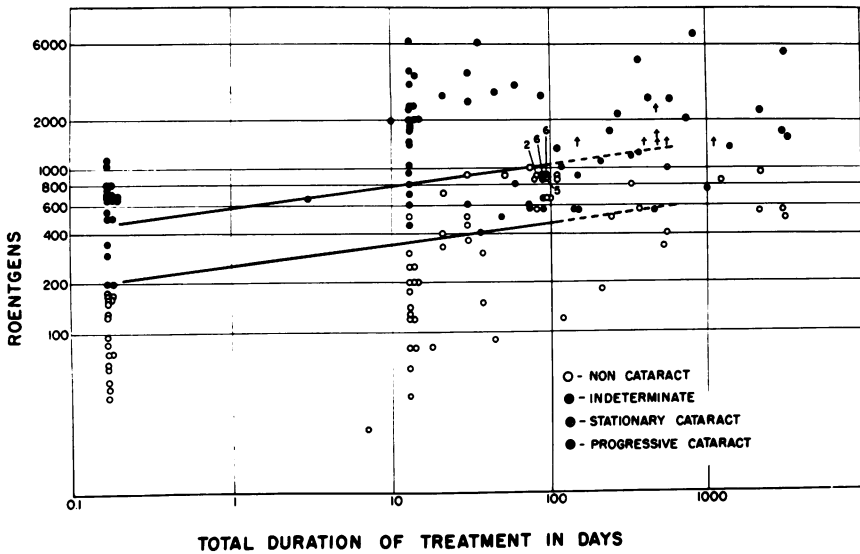


Fig. 3. The dose for the cataract and noncataract cases is shown plotted against the overall treatment time on a log log Strandquist type plot. Each point represents a single case except for those numerically labeled indicating the number of cases occupying a single point. The vertical arrows represent progressive cataracts resulting from doses higher than those indicated but which could not be determined precisely. Indeterminate refers to cataracts in which the stationary or progressive classification could not be determined accurately. Reproduced by permission from Merriam, G. R., Jr., and Focht, E. F.: A clinical and experimental study of the effect of single and divided doses of radiation on cataract production. *Trans. Am. Ophthalmol. Soc.* 60:35-52, 1962

dose combinations that fall above the upper line would usually produce a progressive opacity with visual loss. Those falling below the lower line would not be expected to result in detectable injury to the lens.

Experimental studies have confirmed the clinical observations. Groups of six-month-old, female Columbia-Sherman albino rats were exposed to single and fractionated doses of 500, 1,000, 1,500, and 2,000 rads of 200 kVp x rays. The fractionated doses were delivered in three sessions over six days. The resulting opacities were graded 0 to 4+, the latter representing a completely opaque lens. The mean ratio of fractionated to single dose required to produce a 50% incidence of 2+ cataract over the range of 20 to 50 weeks was 1.34. On a Strandqvist plot (Figure 4) the slope of the line for the rat data was quite similar to that for patients. The results also suggested that fractionation of dose has less effect on the lens than on other tissues. However, the presence of a slope indicates a time-dose relationship for the mammalian lens.

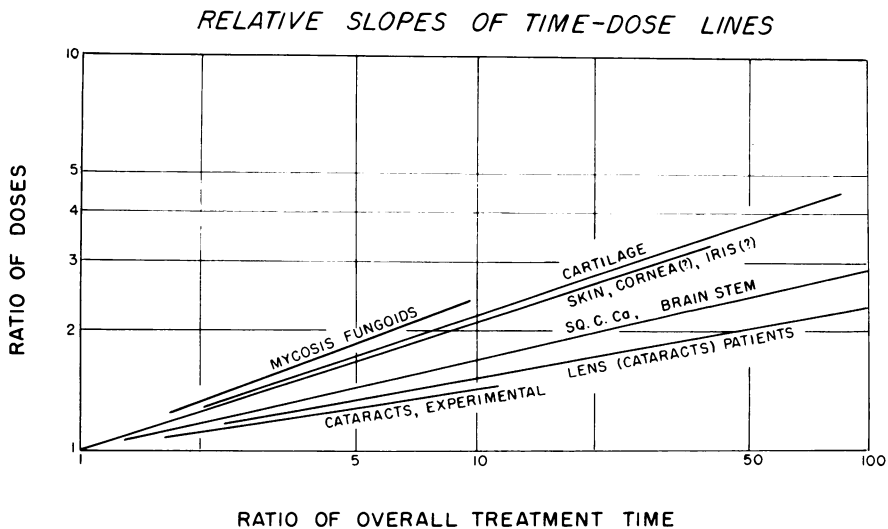


Fig. 4. The mean cataract time-dose curve obtained experimentally and clinically (patients) is compared to those derived from clinical studies of brain stem, skin, Mycosis fungoides, cartilage and squamous carcinoma. Note the shallow slope for cataractogenesis. Reproduced by permission from Merriam, G. R., Jr., and Focht, E. F.: A clinical and experimental study of the effect of single and divided doses of radiation on cataract production. *Trans. Am. Ophthalmol. Soc.* 60:35-52, 1962.

AGE

Soon after the turn of the century, experimental evidence suggested that young lenses might be more sensitive to radiation.^{18,20} From this and subsequent studies arose the current hypothesis that young lenses are much more sensitive to radiation than are adult ones, and, given the same conditions of irradiation, the probability of damage expressed clinically by cataract formation is greater. While this hypothesis was accepted generally, some experimental evidence suggested a more complex age dependence.

An attempt was made to investigate the age problem more fully using larger groups of animals (Columbia-Sherman albino rat) of varying ages. The rats were given single and fractionated doses of radiation and followed for their lifespan or until complete opacification occurred. In these studies approximately 700 animals were utilized.

In general, at dose levels from 200 to 300 rads lens changes occurred sooner and progressed more rapidly in the adult lenses than in the young lenses. In the dose range from 300 rads to 900 rads, opacities developed sooner in the young lenses but progression was faster and severe opacities

developed earlier in the adult lenses. Above 900 rads the opacities developed sooner and progressed faster in the young lenses. It would appear that the increased sensitivity of young lenses is dose-dependent.^{21,22}

RADIATION QUALITY

The biological effect of radiations are in general not directly proportional to the energy deposited in tissue (absorbed dose in rads). The same absorbed doses of 250 kVp x rays, ⁶⁰Co, gamma rays and neutrons may produce varying biological effects. These variations depend also on the tissue under consideration.

In previous studies no difference in the RBE (relative biological effectiveness) was found between ⁶⁰Co and 200 kVp x rays for the production of lens opacities in rats.²³ The RBE of neutrons of various energies for the production of cataracts has been studied extensively in animals. Neutrons were found to be four to 10 times more cataractogenic for a given dose than were x rays.²⁴ The importance of this is demonstrated by the development of cataracts in 10 of 11 physicists exposed to cyclotron neutrons over periods of 10 to 250 weeks. The estimated total accumulated doses at the lens ranged from about 20 to 270 rads, with a median dose of about 100 rads.

These data on the cataractogenic doses of ionizing radiation have become the basis for the radiation protection standards in this country and throughout the world. They also provided the basis for the protection standards for the Apollo flights. In space flight, astronauts are exposed to galactic cosmic radiation and particle fluxes from solar flares. This type of radiation consists of highly charged energetic nuclei with an enormous range of energies, from 100 to over 1,000 MeV/nucleon. Considerable information was available on the physics of these particles but little was known of their biological effects. During the Apollo 11 flight, astronauts reported seeing "light flashes and streaks." These observations were confirmed on subsequent flights and are believed to be due to particles passing through the retina. This was confirmed by Tobias et al.,²⁵ in experiments on their own eyes. The energy of the HZE particles is so great that they pass easily through the capsule and helmets. This led NASA to pose the question: What would be the effect on the vision of the astronauts on prolonged missions of one to two years?

At that time there were no facilities able to produce particles with the

energy of those in space and hence no means to study experimentally the effect of accelerated heavy ions on the eye. However, shortly after the Apollo flights, the BEVALAC facility was developed at the Lawrence Berkeley Laboratory in California. The BEVALAC is a combination of a Bevatron and a SuperHilac (a Heavy Ion Linear Accelerator), which is capable of accelerating ions to energies in excess of 1,000 MeV/amu (million electron volts/atomic mass unit).

In two experiments, conducted one year apart at the BEVALAC, about one thousand four-week-old Columbia-Sherman rats were exposed, to accelerated (570 MeV/amu) ^{40}Ar ions.²⁶⁻³⁰ The rats received whole-head doses ranging from 1 to 350 rads. The cataractogenic potential of the ^{40}Ar ions was compared to animals exposed to low linear energy transfer (LET) radiation of 185 kVp x rays. The x-ray doses ranged from 150 to 1,200 rads. Included in the study were unexposed controls.

It was found that, as is the case with low LET radiation, the time of onset and progression of ^{40}Ar induced cataracts was strongly dose dependent. Also, as is the case with neutrons, the RBE decreased as the dose increased. In general, the opacities were qualitatively similar to those seen with x rays. Histopathologically, at the light and electron microscope level, the effect of the HZE particles was similar to that observed following low LET exposures. Thus, it appears that the accelerated ions in space can be from 3.5 to approximately 100+ times more cataractogenic than conventional x rays, the RBE increasing with decreasing dose.

With an understanding of the basic clinical aspects of radiation cataract comes the obvious question of how radiation produces these characteristic opacities. It is clear that the resolution of this question would provide significant insight not only into the mechanism of radiation cataractogenesis but also into the basic mechanism of a number of cataracts of different etiology. It has been known for a long time that abnormally shaped, often nucleated cells, called Wedl³¹ cells, are associated with radiation cataracts. Prior to the appearance of these cells, the bow region of the lens loses its normal cytoarchitecture. The derangement of the bow is dose-dependent.³²

Historically, a number of hypotheses have been suggested to explain the basis of these pathological changes. The major dichotomy was associated with whether or not the lens is affected directly by radiation. The other aspect is that once affected, either directly or indirectly, which cell population gives rise to the observed pathological changes. The basis of radiation cataract formation then reflected three distinct possibilities: Damage to the

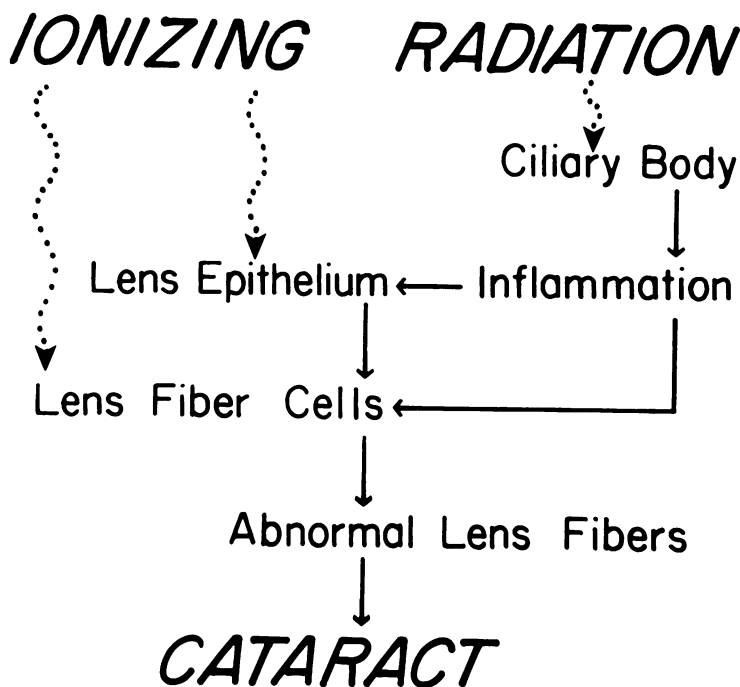


Fig. 5. A schema outlining the historically prevalent views regarding the manner in which radiation was thought to affect the lens to produce cataracts. As shown, the major dichotomy reflected a postulated direct effect on the lens cell populations versus one which depended upon a primary effect on the ciliary body. It was believed that an intraocular inflammation caused by ciliary body damage might secondarily influence one or the other of the lens populations thought to be at risk. In any case, it was clear that abnormal lens cells appear and that these are the first cytopathological correlates to clinically detectable opacities.

ciliary body resulting in inflammation and an altered aqueous humor, thus indirectly affecting the lens; injury to the lens fibers directly; and injury to the lens epithelium resulting in the formation of abnormal lens fibers. A schema illustrating these possibilities is shown in Figure 5.

DAMAGE TO THE CILIARY BODY

Our attention was directed first to the ciliary body because if, indeed, this is the site of injury, further studies would necessarily be directed toward the effects of inflammation of the lens. Recent studies in our laboratory have shown that irradiation of rabbit eyes with cataractogenic doses of x rays produced an early, short-lived intraocular inflammation similar to endotoxin induced uveitis.³³ This observation, as well as earlier

studies by others, suggested a correlation between radiation-induced inflammation and cataractogenesis. Further, the biomicroscopic and histological similarities of cataracts arising secondary to nonspecific intraocular inflammation and those following x-irradiation^{5,16,32,34} further intimated that radiation-induced inflammation might be important in the development of radiation opacities.

Studies were done to assess this question.³⁵ In the rat it was found that only x-ray doses greater than 1,800 rads produced ocular changes consistent with uveitis beginning one to four days postirradiation. Low to moderate cataractogenic doses (200-1,200 rads) failed to produce inflammation.

In rabbit eyes, a single 1,000 rad dose of x rays induced inflammation and cataract. However, when the same dose was divided into 10 100 rad daily fractions there was no inflammation and yet the cataracts were similar in appearance and time of onset to those induced by the single 1,000 rad dose.

In another series of experiments the nasal half of the rabbit eye was shielded and the exposed lateral half irradiated with a single dose of 1,000 rads. Direct measurements showed that the shielded half received less than 10 rads. These eyes developed typical inflammatory changes throughout the anterior segment but the cataracts that developed were localized to the unshielded half of the lens. These and other studies suggest that a mediating inflammation is not essential to the development of an x-ray cataract.

DIRECT INJURY TO THE LENS FIBERS

A schematic diagram of the lens is shown in Figure 6. Because the early stages of radiation cataract are associated with the presence of abnormal fibers located posteriorly beneath the capsule, a favored hypothesis was that existing fibers were damaged by the x rays and became misshapen as they degenerated. This position was generally accepted because it was then believed³⁶ that cells in the germinative zone at the time of irradiation do not enter the lens substance as fibers prior to the appearance of the cataract.

Studies in our laboratory showed the contrary to be true.³² In a series of experiments it was shown that cells in the germinative zone, labeled with tritiated thymidine before radiation, differentiate and are displaced into the posterior cortex well before the earliest clinically detectable opacities are

HUMAN LENS

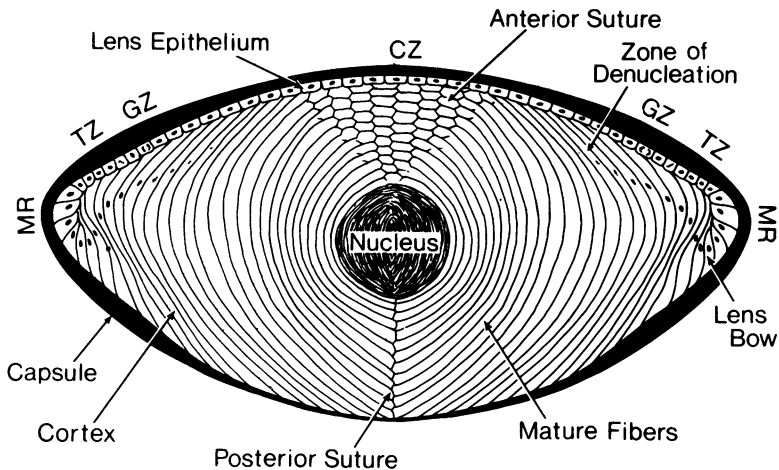


Fig. 6. A diagram of a sagittal section of a human lens illustrating the various cellular relationships in that tissue. MR = Meridional Rows, GZ = Germinative Zone, TZ = Transitional Zone, CZ = Central Zone.

evident. More recent studies in which lenses were irradiated at various times after tritiated thymidine administration to allow labeled cells to reach predetermined stages of differentiation showed that labeled cells in the meridional rows at the time of exposure were not among the cells which migrated posteriorly. In fact, they differentiated into morphologically normal fibers and occupied their usual position in the bow. Therefore, the progenitors of the aberrant fibers in the posterior cortex are cells that were in the epithelium at the moment of irradiation.

INJURY TO THE LENS EPITHELIUM AND MERIDIONAL ROWS

It is apparent from the previous discussion that the primary site of injury from radiation is the epithelium. However, it remains to be determined which cell population was primarily affected, the central zone, germinative zone, or meridional rows.

The central zone is essentially nonmitotic, although cell division can be induced by a variety of means.³⁷ In experiments in a number of laboratories,³⁸⁻⁴³ doses from 4,000 to 30,000 rads were delivered to the central zone with the rest of the lens shielded, and no opacities resulted.

It has long been recognized that actively dividing cells are the most radiosensitive. The primary site of mitotic activity in the lens is the germinative zone of the lens epithelium (see Figure 6). This is the band of cells located pre-equatorially. The equatorial cells are the differentiating progeny of the germinative zone population. Following a terminal cell division, the epithelial cells begin differentiation and form the meridional rows. Here the cells queue up in precise register, forming orderly columns of nuclei.

Many investigators have shown that the germinative zone must be irradiated for a cataract to develop.^{32,38,39,44,45,46} A marked depression of mitotic activity occurs soon after irradiation. This is followed by an overshoot with a gradual return to normal. This period of mitotic depression persists for varying periods depending upon the animal and the dose.^{45,47}

It is clear that cell division is required for the development of radiation cataracts. Leinfelder and Dickerson⁴⁸ showed that mitosis was eliminated for six months following irradiation of the ground squirrel lens and that cataracts did not develop during that period.

In a series of studies,⁴⁶ lenticular mitosis was controlled in frogs by the use of the mitogenic⁴⁹ hormone triiodothyronine (T₃) and temperature.⁵⁰ It was shown that not only is mitosis intimately involved in radiocataractogenesis but that postirradiation proliferative activity is absolutely essential for cataract formation. Even when the number of divisions is high at the time of exposure, a cataract will not develop if subsequent mitosis is suppressed. If mitosis is later allowed to resume, cataracts develop, albeit at a muted rate.

In more recent experiments utilizing hypophysectomy to eliminate mitotic activity, putuitary-deprived frogs did not develop radiation cataracts.⁵¹ Interestingly, the cytological damage to the differentiating cells of the meridional rows typically associated with radiation damage failed to materialize.⁵²

In the 1890s Rabl^{53,54} described in detail the highly ordered arrangement of cells in the meridional rows (Figure 7). An adequate explanation for this unique organization has not been forthcoming. There is little doubt, however, that this precise alignment of elongating epithelial cells is important to the maintenance of normal cytoarchitecture and, therefore, transparency. Loss of this alignment has been associated with a number of different types of cataracts. Studies indicate that after moderate doses of x rays, the beginning of such meridional row disorganization (Figure 8) in

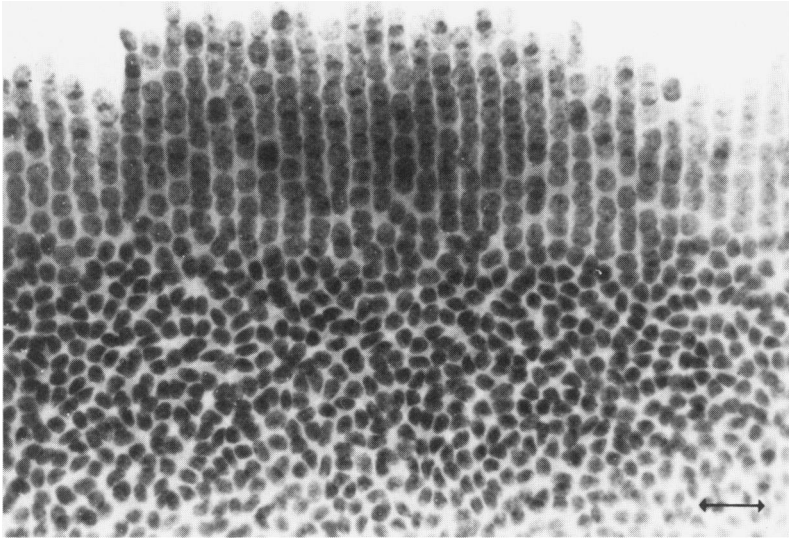


Fig. 7. A photomicrograph of meridional rows in the rat lens. Note the precise register of the nuclei of the cells. H & E. Scale marker equals 20 μ m.

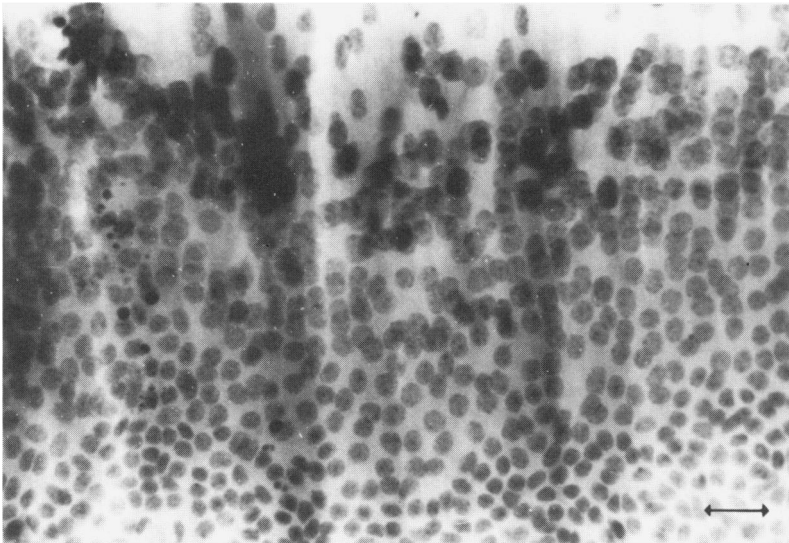


Fig. 8. Meridional rows as they appear two weeks after exposure of the rat lens to 1,000 rad x rays. The disorganization of the rows is evident. The cells occupying the rows were in the germinative zone at the moment of irradiation. H & E. Scale marker equals 20 μ m.

the rat lens corresponds to the time that the first epithelial cells from the germinative zone appear in the rows. This is also the case in frogs.⁵² Other investigations showed that the severity of the radiation cataract is strictly correlated to the degree of disorganization of the rows. In fact, meridional row disorganization following radiation predates the appearance of a cataract by sufficient time that the degree of disruption can be used as a gauge of the severity of the cataract that follows.⁴⁶ It must be noted that the cells of the meridional row are, in fact, the most superficial row cells as viewed from the perspective of an epithelial whole-mount preparation.

This effect of radiation on the meridional rows is, as is cataract development, dose-dependent. The higher the dose, the more severe the disorganization and the earlier it will appear. This clearly implicates the germinative zone cell in the cytopathological changes preceding cataractogenesis, but the studies do not eliminate the possibility that some factors within the rows themselves become altered and secondarily cause the misalignment of the incoming epithelial cells.

Radiation is not the only cataractogenic agent to affect the meridional rows. Cataracts of congenital origin, those produced by alkylating agents, inflammation, and aging are associated with meridional row disorganization.⁵⁵ Thus, if one could understand the basis for this loss of organization as the result of radiation exposure, our understanding of the mechanism associated with other cataractogenic agents would be furthered.

Studies have shown that radiation of a young rat lens with doses exceeding 200 rads causes, within hours, fragmentation of the nuclei of some of the cells in the meridional rows.⁵⁶⁻⁶⁰ This is a direct effect on cells in the meridional rows. The numbers of fragmented nuclei, when observed at the peak time of 12 hours after irradiation, reveal a strong dose dependence.⁵⁸ A dose of 400 rads will produce less than one damaged nucleus in 10 rows while 2,400 rads result in one fragmented nucleus for every two rows. Time-course analysis showed that the time of onset is inversely related to dose. Fragmented nuclei appeared 4.5 hours following 2,400 rads and appeared nine hours after 600 rads. Other studies were age-dependent.⁵⁹ That nonmitotic cells of the meridional rows are affected suggests that the pathological change can be described as interphase death. Although nuclear fragmentation is strongly dose-dependent, as is cataractogenesis, and the thresholds for each are similar, it seems unlikely that interphase death plays a role in cataract development.

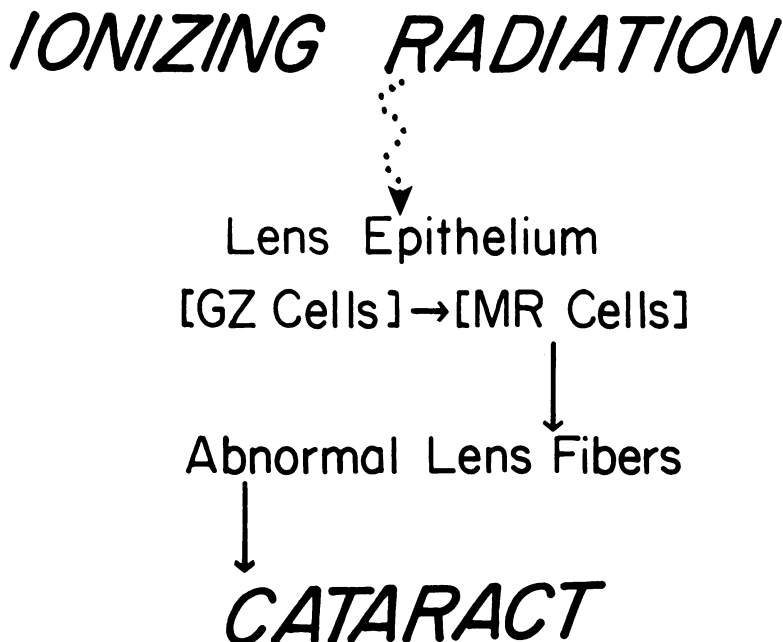


Fig. 9. A diagram illustrating the current view of the manner in which ionizing radiation acts to produce cataracts. While an effect on the cells of the Germinative Zone is certain, the possible contribution of direct damage to the Meridional Rows to the overall process is still problematic.

DEVELOPMENT OF RADIATION CATARACT

As a result of the investigative work just described, the hypothetical actions of radiation on the lens have been reduced from those shown in Figure 5 to those illustrated in Figure 9. We now believe that radiation cataracts develop in the following manner: The initial injury is suffered primarily by epithelial cells in the germinative zone. When these cells resume mitosis their progeny are displaced into the meridional rows where damage is expressed by an altered differentiation reflected in the disorganization of the rows. The exact mechanism for this disruption is not apparent as yet. In any event, the precise order of the rows is disrupted and nucleated, abnormally shaped fibers begin to accumulate beneath the posterior capsule. In the posterior subcapsular region these cells assume a rounded, bladderlike appearance and are known as "Wedl" cells. Nuclei of these cells are often pycnotic. Later, the Wedl cells may rupture, leaving eosinophilic material and cellular debris strewn between apparently intact cells. While these changes are occurring in the posterior

superficial cortex, deeper fibers seem morphologically unaffected at this time. Eventually, abnormally shaped cells begin to appear anteriorly and the accumulation of these can completely surround the deeper cortex. It is the abnormal cytoarchitecture of the lens cortex caused by these aberrant cells that interferes with the transmission of light and seems to be the basis for the initial opacities.

The lens is a unique structure in that it has no blood supply and is enclosed in a capsule. Thus, there is no mechanism for removing cellular debris. In addition, the lens can be regarded as a syncytium.^{61,62} The fibers are in intimate contact by virtue of gap junctions upon which the survival, particularly of the deeper fibers, are thought to depend. When the superficial cortex becomes enclosed by the newly formed abnormal fibers, normal metabolic activity is disrupted and the deeper cortex and eventually the entire lens opacifies.

When chronic inflammation is the cataractogenic agent, the initial injury to the epithelium is indirect through the altered aqueous humor. In the cortical variety of senile cataract, the epithelial cells, for reasons not yet understood, begin to produce abnormal fibers. In this type of cataract, Streeten and Eshagian⁶³ have shown that the disorganization of the meridional rows is identical with that found in radiation cataract. Thus, it appears that although the initial injury to the epithelium may vary, the end result is similar.

SUMMARY

Radiation cataract, a type of complicated cataract, has proved a useful model for studying the mechanisms involved in the development of senile opacities. The initial insult is to the lens epithelium with subsequent disorganization of the meridional rows and the appearance of the abnormal nucleated fibers (Wedl cells) posteriorly.

Experimental studies involved in the formation of our present understanding of cataract development are detailed. Much remains to be done but it would appear that the opacification process is primarily the result of basic changes in the epithelial cells.

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